REMARKS

Upon entry of this amendment, Claims 1, 4, 5, 7-17, 25-27, 29, 31, 33, 35, 37-52, 56, 58, 61, 62, 64, 66, 69, 70, 72, 74, 76, 78, 80, 82, 84, 86-88, 91, 93, 95, 97, 99, 101, 103-111, 113, 115, 117, 119, 121, 123, 125, 127-138, 147, 148, 150, 151, and 156 (renumbered from the former 2nd Claim 104) constitute the pending claims in the present application. Among them, Claims 39, 45-51, 56, 61, 62, 64, 87, 88, 103-106, 109-111, 121, 123, 125, 135-138, 147, 148, 150, and 151 are directed to non-elected inventions or species, and are withdrawn from further consideration.

Claim 2, 3, 6, 18-24, 28, 30, 32, 34, 36, 53-55, 57, 59, 60, 63, 65, 67, 68, 71, 73, 75, 77, 79, 81, 83, 85, 89, 90, 92, 94, 96, 98, 100, 102, 112, 114, 116, 118, 120, 122, 124, 126, 139-146, 149, and 152-155 are canceled without prejudice. Applicants reserve the right to prosecute claims of identical or similar claims in future continuation or divisional applications.

Applicants note that withdrawn Claims 135-138, 147, 148, 150, and 151 are directed to methods of use / making the elected product claims. Pursuant to MPEP 821.04(b), "[w]here claims directed to a product and to a process of making and/or using the product are presented in the same application, applicant may be called upon under 35 U.S.C. § 121 to elect claims to either the product or a process ... if applicant elects a claim(s) directed to a product which is subsequently found allowable, withdrawn process claims which depend from or otherwise require all the limitations of an allowable product claim will be considered for rejoinder ... Upon rejoinder of claims directed to a previously nonelected process invention, the restriction requirement between the elected product and rejoined process(es) will be withdrawn."

Therefore, upon indication of allowable product claims such as Claim 5, these method of use / making claims which depend from or otherwise require all the limitations of the allowable product claim should be considered for rejoinder.

In addition, as the Office Action indicates, upon the indication of allowability of the linking claims, the restriction requirement as to the linked inventions shall be withdrawn, and any claims depending from or otherwise requiring all the limitations (such as the withdrawn (dependent) claims directed to non-elected species) of the allowable linking claims will be rejoined and fully examined for patentability. Presently, withdrawn claims 39, 45-51, 56, 61, 62,

64, 87, 88, 103-106, 109-111, 121, 123, and 125 depend from one or more linking claims under examination.

Applicants note that the IDS received on November 26, 2003, July 5, 2005, September 29, 2005, and March 24, 2006, have been considered by the Examiner. Applicants hereby submit an additional supplemental IDS, and respectfully request consideration by the Examiner.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim objections

The Office Action objects to the presence of two "Claim 104," and requests correction.

Accordingly, Applicants have renumbered the second (2nd) "Claim 104" as Claim 156 to obviate this objection. Reconsideration and withdrawal of the objection are respectfully requested.

Applicants note that it is the present Claim 156 (former 2nd Claim 104) that is currently under consideration. Claim 104 is withdrawn from further consideration.

The Office Action objected to Claims 99 and 100 for having typographic mistakes. Accordingly, Applicants have corrected these mistakes to obviate the objection. Applicants submit that these amendments do not narrow the scope of the claims.

Claim Rejections under 35 U.S.C. § 112, second paragraph

The Office Action rejects Claims 1, 2, 4-27, 29, 31, 33, 35, 37, 38, 40-44, 52, 53, 58, 60, 66, 68-82, 84-86, 90-102, 107, 108, 113-120, 127-134, and 156 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Specifically, the Office Action rejects Claims 1, 10, and 11, as allegedly being confusing because these claims recite "potency," the meaning of which is allegedly unclear.

Applicants submit that "potency" is a term-of-art commonly used in biochemistry and enzymology to refer to enzyme activity. For example, in the cited art Holvoet (see below), the authors repeatedly used "potency" in, for example, the right column of page 19717. Thus Applicants submit that a skilled artisan would readily understand the meaning of the term.

The Office Action rejects Claims 27, 29, 31, and 33 for failing to provide antecedent basis for "said linker."

Accordingly, Applicants have amended these claims to provide proper antecedent basis.

The Office Action rejects Claims 8 and 9 for allegedly being indefinite, since "it is unclear what define 'abundant.'"

Applicants have amended Claims 8 and 9 to obviate this rejection.

The Office Action also rejects Claim 8 for allegedly lacking antecedent basis for "the target molecule." Applicants have amended Claim 8 to obviate this rejection.

The Office Action also rejects Claim 8 for allegedly being confusing, because it recites "wherein the effect of the adzyme on the substrate is effective against the target molecule." Applicants have amended Claim 8 to obviate this rejection.

The Office Action also rejects Claim 60 for allegedly being confusing, because it recites "pendant groups," the meaning of which is allegedly unclear.

Solely to advance prosecution, Applicants have canceled Claim 60 without prejudice.

Applicants submit that all pending claims satisfy the requirements of 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 4-27, 29, 31, 33, 35, 37, 38, 40-44, 52, 53, 58, 60, 66, 68-82, 84-86, 90-102, 107, 108, 113-120, 127-134, and 156 are rejected under 35 U.S.C. § 112, first paragraph, because "the specification, while being enabling for an adzyme or bifunctional fusion protein wherein prethrombin is conjugated via a linker with scFvαHA (antibody) or trypsin is conjugated via a linker with sp55 of TNFR1 or anti-TNFα scFv antibody, does not reasonably provide enablement for any adzyme or fusion protein of any antibody, protein, peptide or chemical molecule with any enzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims."

Specifically, the Office Action argues that the claims covers "extreme large number (of) adzymes...Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved, and detailed knowledge of the ways in which the protein's structure relates to its function."

Applicants have amended independent Claims 1 and 5 to clarify the subject matter claimed. Applicants have also amended most of the dependent claims so that they directly or indirectly depend on Claim 5.

Applicants note that the amendments to Claim 5 are solely for the purpose of providing proper antecedent basis, and does not narrow the scope of the claim.

Applicants submit that the presently claimed invention relates to adzymes with distinct, functional *domains*, rather than fusion proteins with *mutagenized* functional domains. While it may be true that protein structures and functions, after *intra*-domain mutagenesis, may be somewhat less predictable, this is usually not the case when different protein domains are fused together to create novel fusion proteins, such as in the instant claimed invention. This is because in the claimed fusion proteins, the functional domains (such as the recited catalytic domain and the targeting domain), remains largely intact. Thus contrary to the Examiner's suggestion, there is usually no need to know which amino acid changes can be tolerated in the fusion protein, since there is usually no such changes in the functional domains. Any changes in the linker sequence are not expected to alter the folding of the catalytic or targeting domain.

This is much like the very mature yeast two-hybrid assay (see, for example, U.S. Pat. No. 5,283,173), in which a functional DNA-binding domain is fused to a first polypeptide ("bait"), and a functional transcriptional activation domain is fused to a *library* of "prey" polypeptides. Transcription of a reporter gene can be activated if the bait binds a prey in the library. Similarly, GST-fusion technology has been routinely used in biochemistry to produce and purify almost *any* protein fused to the GST-domain (*e.g.*, the GST domain rarely ever loses its binding ability when fused with *any* polypeptide).

One major reason why the two-hybrid assay works is that the functional DNA-binding domain and the functional transcription activation domain can usually maintain their respective functions, *regardless of which polypeptides they are fused with.* Thus almost *any* protein may

serve as a "bait" without losing its ability to bind its prey, when the bait is fused with the DNA-binding domain (or the transcription activation domain). It is usually not necessary to know, before constructing the bait fusion, "knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved." In fact, such knowledge is not required even for the structurally much less predictable prey-library, in which many encoded fusion proteins may not even be functional.

In the instant case, a functional catalytic domain is fused with a functional targeting domain to create an adzyme with novel functionality. If the prior art technology enables the much more technically demanding yeast two-hybrid assay, the instant specification certainly have provided sufficient disclosure to enable the subject adzymes.

In addition, although the amended claims are not limited to a specific catalytic domain, for any *chosen* catalytic domain (such as trypsin) that an artisan desires to put into an adzyme, there is no need for screening "multiple substitutions or multiple modifications" as the Office Action suggests.

Therefore, all pending claims satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejections are respectfully requested.

The Office Action also rejects Claims 1, 2, 4-27, 29, 31, 33, 35, 37, 38, 40-44, 52, 53, 58, 60, 66, 68-82, 84-86, 90-102, 107, 108, 113-120, 127-134, and 156 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action argues that the claimed invention is directed to a broad genus of adzymes, while the specification provides only "a few" such fusion proteins and no other representative species.

Applicants submit that the final guidelines for 35 U.S.C. § 112 clearly state that there is a *strong presumption* that the specification as filed provides adequate written description support for the claimed invention. MPEP 2163.03 also states that "rejection of an original claim for lack of written description should be rare." A disclosure as filed is *prima facie* adequate.

Also pursuant to MPEP 2163.02: "An objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'... Whenever the

issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.... An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention.... Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete." (emphasis added).

In view of the guidelines recited above, and the reasoned proffered below, Applicants respectfully submit that the written description requirement is met for the claimed invention.

Inverse correlation between level of skill and specificity of disclosure: "The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed (see, *e.g.*, *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification. See, *e.g.*, *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)." (emphasis added, see MPEP 2163, Section II(A)(2)).

Applicants submit that the level of skill and knowledge in the art regarding construction of fusion protein with functional domains (*e.g.*, a catalytic domain and a targeting domain) is very high, thus there is no need to describe numerous adzymes in detail in the specification.

Although different adzymes may have biochemically different catalytic domains and targeting domains, the process of constructing fusions are largely the same. This is somewhat like the construction of a cDNA library – although the cDNAs encode vastly different proteins, ligating such cDNAs into a plasmid vector involves essentially the same kind of manipulation. This is also somewhat like the construction of the DNA binding domain – bait construct in the

yeast two-hybrid assay. Although the bait can be virtually any of a diverse array of proteins, almost all baits can be successfully linked to the DNA binding domain to form a functional two-hybrid construct.

Therefore, the several described adzymes are indeed representative species of the claimed genus. A skilled artisan can readily envision and construct other adzymes with any other catalytic and targeting domains for a desired substrate.

Possession by description: Applicants have also shown possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. For example, Section III of the specification goes into details to describe the various parts of the adzymes, including the design of linkers, using figures, formulas, tables, and specific examples. Pages 110-112 provide details regarding the various ways one can make adzymes resisting cleavage by the catalytic domain, which is an important feature of the presently claimed invention.

Possession by example: Furthermore, Applicants have demonstrated possession of the claimed invention by describing examples of actual reduction to practice. For example, Examples 2 and 3 (and the associated figures) of the specification provide details regarding the construction, expression, purification, and biochemical characterization of several representative adzymes. A skilled artisan can readily produce other adzymes with minor modifications.

In summary, the instant specification provides adequate written description for the claimed adzymes, and all pending claims satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim Rejections under 35 U.S.C. § 102

The Office Action rejects Claims 1, 2, 5-11, 25, 35, 37, 38, 40-42, 44, 52, 53, 66-82, 84, 85, 90-98, 107, 108, 127, and 133 under 35 U.S.C. § 102(b) as allegedly being anticipated by Holvoet *et al.* (JBC 266: 19717-24, 1991, "Holvoet"). Specifically, the Office Action argues that Holvoet teaches a plasminogen activator – fibrin-specific antibody fusion protein.

Applicants submit that independent Claim 5 and the amended Claim 1 require the

claimed adzyme to be resistant to cleavage by its catalytic domain. The Office Action fails to point out which passages in Holvoet teaches or suggests such a claimed feature. Thus Holvoet cannot anticipate the claimed invention, and rejection to Claim 5 is improper. Reconsideration and withdrawal of the rejection are respectfully requested.

The Office Action rejects Claims 2, 4-9, 11-28, 31, 35, 37, 38, 40-44, 52, 53, 58, 60, 66, 68-82, 84-86, 90-102, 107, 108, 113-120, 127, 128, and 156 under 35 U.S.C. § 102(b) as allegedly being anticipated by Davis *et al.* (WO 00/64485, "Davis"). Specifically, the Office Action argues that Davis teaches a serine protease – ligand binding domain fusion protein, optionally with a linker.

Applicants submit that independent Claim 5 and the amended Claim 1 require the claimed adzyme to be resistant to cleavage by its catalytic domain. The Office Action fails to point out which passages in Davis teaches or suggests such a claimed feature. Thus Davis cannot anticipate the claimed invention, and rejection to Claim 5 is improper. Reconsideration and withdrawal of the rejection are respectfully requested.

The Office Action rejects Claims 2, 4-9, 11-28, 31, 36, 37, 38, 40-44, 52, 53, 58, 60, 66, 68-82, 84-86, 90-102, 107, 108, 113-120, 127, 128, and 156 under 35 U.S.C. § 102(e) as allegedly being anticipated by Chen *et al.* (US 2003/0068792, "Chen"). Specifically, the Office Action argues that Chen teaches an enzyme – Ig fusion protein.

Applicants submit that independent Claim 5 and the amended Claim 1 require the claimed adzyme to be resistant to cleavage by its catalytic domain. The Office Action fails to point out which passages in Chen teaches or suggests such a claimed feature. Thus Chen cannot anticipate the claimed invention, and rejection to Claim 5 is improper. Reconsideration and withdrawal of the rejection are respectfully requested.

The Office Action rejects Claims 1 and 10-24 under 35 U.S.C. § 102(b) as allegedly being anticipated by Holvoet and Chen.

However, as argued above, neither Holvoet nor Chen anticipates the amended claims for lack of at least one claimed feature. Thus reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 are respectfully requested.

Double Patenting Rejection

The Office Action states that Claims 4 and 5 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 2, 19, and 35 of the co-pending U.S. Application Nos. 10/792,498 and 10/650,591. Similarly, the Office Action also rejects other claims of the instant application on the ground of obviousness-type double patenting over various claims in these two co-pending U.S. applications.

Applicants submit that before amendment, pursuant to MPEP 804, "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent [without filing a terminal disclaimer], thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent." Thus Applicants respectfully request the Examiner to hold the provisional double patenting rejection in abeyance until the indication of allowable subject matter in this or the other co-pending applications.

If conflicting claims are first allowed in these two co-pending U.S. Applications, and appear in an issued U.S. patent, Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. The Director is hereby authorized to charge any other deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **18-1945**, under Order No. **COTH-P01-001**.

Dated: September 29, 2006

Respectfully submitted,

By_____

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